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Copper-catalyzed Eglinton oxidative homocoupling of terminal alkynes: A computational study

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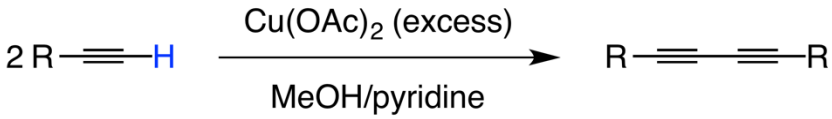
Abstract

The copper(II) acetate mediated oxidative homocoupling of terminal alkynes, namely the Eglinton coupling, has been studied with DFT methods. The mechanism of the whole reaction has been modeled using phenylacetylene as substrate. The obtained results indicate that, in contrast to some classical proposals, the reaction does not involve the formation of free alkynyl radicals and proceeds by the dimerization of copper(II) alkynyl complexes followed by a bimetallic reductive elimination. The calculations demonstrate that the rate limiting-step of the reaction is the alkyne deprotonation and that more acidic substrates provide faster reactions, in agreement with the experimental observations.

Introduction

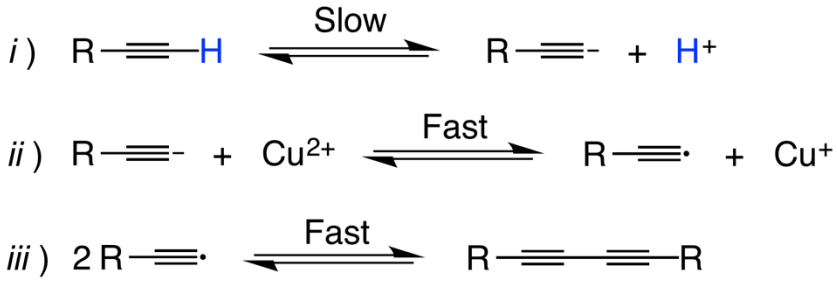
Conjugated diynes are recurring building blocks in a great range of industrial intermediates and materials.[1-5] Besides their very well known antifungal properties,[6] they have been widely employed to prepare optical[7] and organic materials,[8-10] and molecular devices.[7,11] Acetylenic coupling has become a powerful tool to obtain 1,3-diynes and has experienced a great development in recent years. Nevertheless, the first acetylenic coupling dates from 1869 and was reported by Glaser, he observed that copper(I) phenylacetylide smoothly underwent homocoupling under aerobic conditions to deliver diphenyldiacetylene.[12,13] This process was further developed later, the so-called Hay modification, by including nitrogen donor ligands such as N,N,N',N'-tetramethylethylenediamine (TMEDA) which facilitated the whole process and allowed to carry out the reaction under homogeneous conditions.[14,15] Some years later other similar catalytic procedures, leading to asymmetric diynes, were proposed *e.g.* the Sonogashira[16,17] and Cadiot-Chodkiewicz[18] cross-coupling reactions. However, many of these protocols require expensive metal sources and external oxidants in order to recover the active catalyst, which clearly is a disadvantage. One way to circumvent this issue is using the copper-mediated oxidative homocoupling of terminal alkynes was reported by Eglinton and Galbraith in the late 1950s.[19,20] This reaction, shown in a general form in Scheme 1, employs the inexpensive copper(II) acetate as the metal source in a (super)stoichiometric amount. This coupling is usually fast, clean, completely

homogeneous and tolerates mild reaction conditions. The solvent of choice is usually a 1:1 methanolic pyridine mixture, but other solvents can be employed. In addition, unlike many other metal-mediated reactions the Eglinton coupling does not require the usage of any other external ligand.



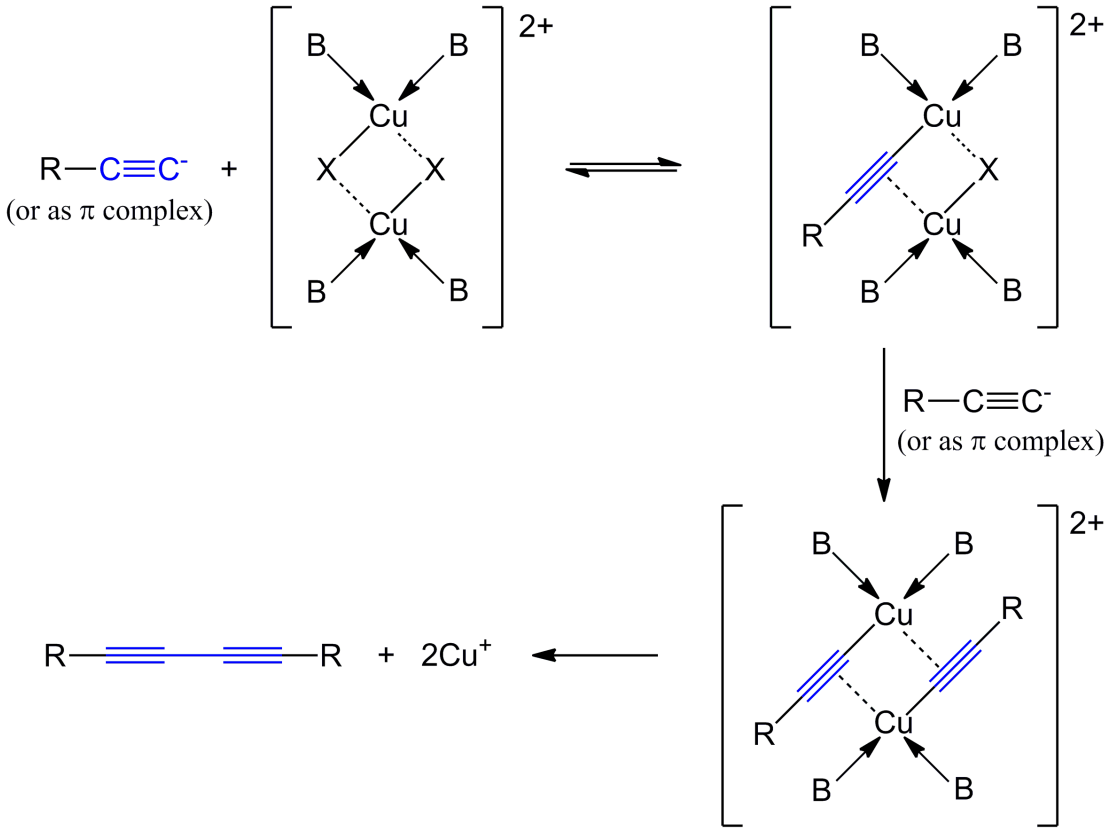
Scheme 1. General form of the Eglinton oxidative homocoupling of alkynes.

In recent years the Eglinton reaction has been widely employed in the synthesis of cyclic bisacetylenes[21-23] and macrocycles[24,25] such as annulenes,[26,27] rotaxanes,[28] catenanes,[29,30] conjugated long structures,[31] poly$_n$-diyls[32] and molecular wires.[11] Although this coupling method has been known for a long time and is still widely applied, the mechanism governing this reaction is not completely understood. The first mechanistic proposal was reported by Salkind *et al.*,[33] Scheme 2. In there, the terminal alkyne is deprotonated (step *i*) and then oxidized by copper(II) to form the alkynyl radical (step *ii*) than can afterwards dimerize to deliver the final 1,3-diyne (step *iii*). The authors propose that the first two stages probably involve copper derivatives rather than isolated anions and indicate that the rate-limiting step is the first one, based on experimental observations that state that the most acidic acetylenes provide the fastest reactions.[34]



Scheme 2. Cu(OAc)$_2$-mediated oxidative homocoupling of terminal alkynes, as proposed by Salkind *et al.*.

Nevertheless, it has never been demonstrated that the reaction follows a radical mechanism and the identity of the base remains to be determined since in some reports this role is attributed to the acetate ligands but other sources propose the pyridine solvent as the deprotonating agent. Some years later a more elaborated proposal was reported by Bohlmann and co-workers,[35] Scheme 3. Based on their scheme, the reaction starts with the π-coordination of the triple bond to a copper species, facilitating the activation of the terminal C–H bond by a base. The final diyne product is obtained by reductive elimination from a “dinuclear” copper(II) acetylide species.



Scheme 3. Bohlmann proposal for the copper-mediated coupling of acetylenes (B = N ligand).

In this report the mechanism of the Eglinton oxidative homocoupling of terminal alkynes is studied aiming to determine if the proposed mechanisms are plausible; the radical character of the reaction as well as the nature of the base and the substrate influence oin the reaction rate will be also studied. Other similar copper-catalyzed reactions have been studied computationally with very successful outcomes,[36-39] showing the value of computational approximations on mechanistic studies of this kind.

Computational details

All the structures have been fully optimized using the Gaussian09 package,[40] with the B97D density functional.[41,42] This functional has been successfully employed in other computational reports involving similar systems to the one studied in this communication.[43,44] All the calculations involving radical systems, such as those including copper(II) cations, have been performed using unrestricted wavefunctions.

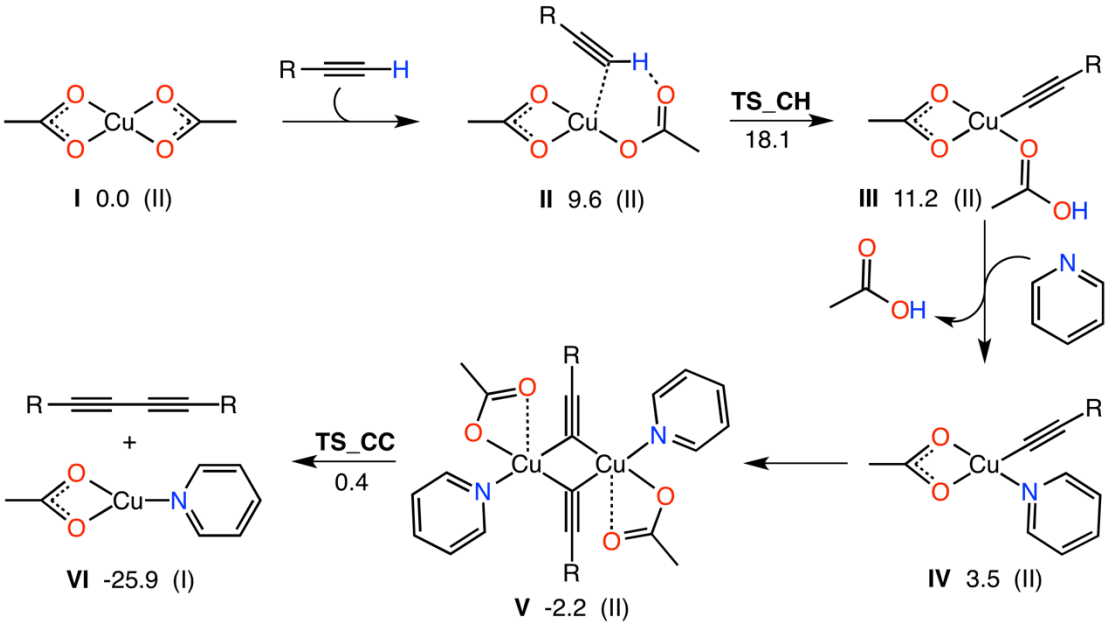
In the optimization process the standard 6-31G(d)[45-47] basis set was used for all H, C, N and O atoms while the Stuttgart triple zeta basis set (SDD),[48,49] along with the associated ECP to describe the core electrons, was employed for Cu. All the optimizations have been carried out in solvent employing the (IEF-PCM) continuum dielectric solvation model[50,51] including the radii and non-electrostatic SMD terms developed by Truhlar and coworkers.[52] Experimentally, a 1:1 mixture of pyridine and methanol was employed as solvent. In the calculations only the former was used

because using a mixture of solvents in Gaussian09 is not allowed and, in addition, pyridine is used sometimes as an explicit ligand. Nevertheless, the impact of using pyridine alone on the calculated free energies is expected to be small. In all cases frequency calculations were carried out to ensure the nature of stationary points and transition states.

Additional single point calculations on the previously optimized geometries were employed to obtain improved solvated free energy values with larger basis sets. The aug-cc-pVTZ-PP basis set including polarization and the associated electron core potential[53] was employed for Cu while the 6-311+G** all-electron basis set[47,54,55] was used for all the other atoms. The solvation model is maintained the same as in the optimization process. Unless otherwise stated all the free energy values in the text correspond to those obtained with the larger basis sets including solvation at 25ºC.

Results and discussion

In this section the most plausible mechanism for the Eglinton oxidative homocoupling of phenylacetylene, a representative sample of the terminal alkynes usually employed, is described (Scheme 4). Alternative pathways have been computed whenever possible in order to check that the best option is always selected. The detailed structures of all the computed copper intermediates can be found in Figure 1.



Scheme 4. Proposed catalytic cycle for the Eglinton reaction (free energies in kcal mol^{-1}, the copper oxidation state is given between parentheses).

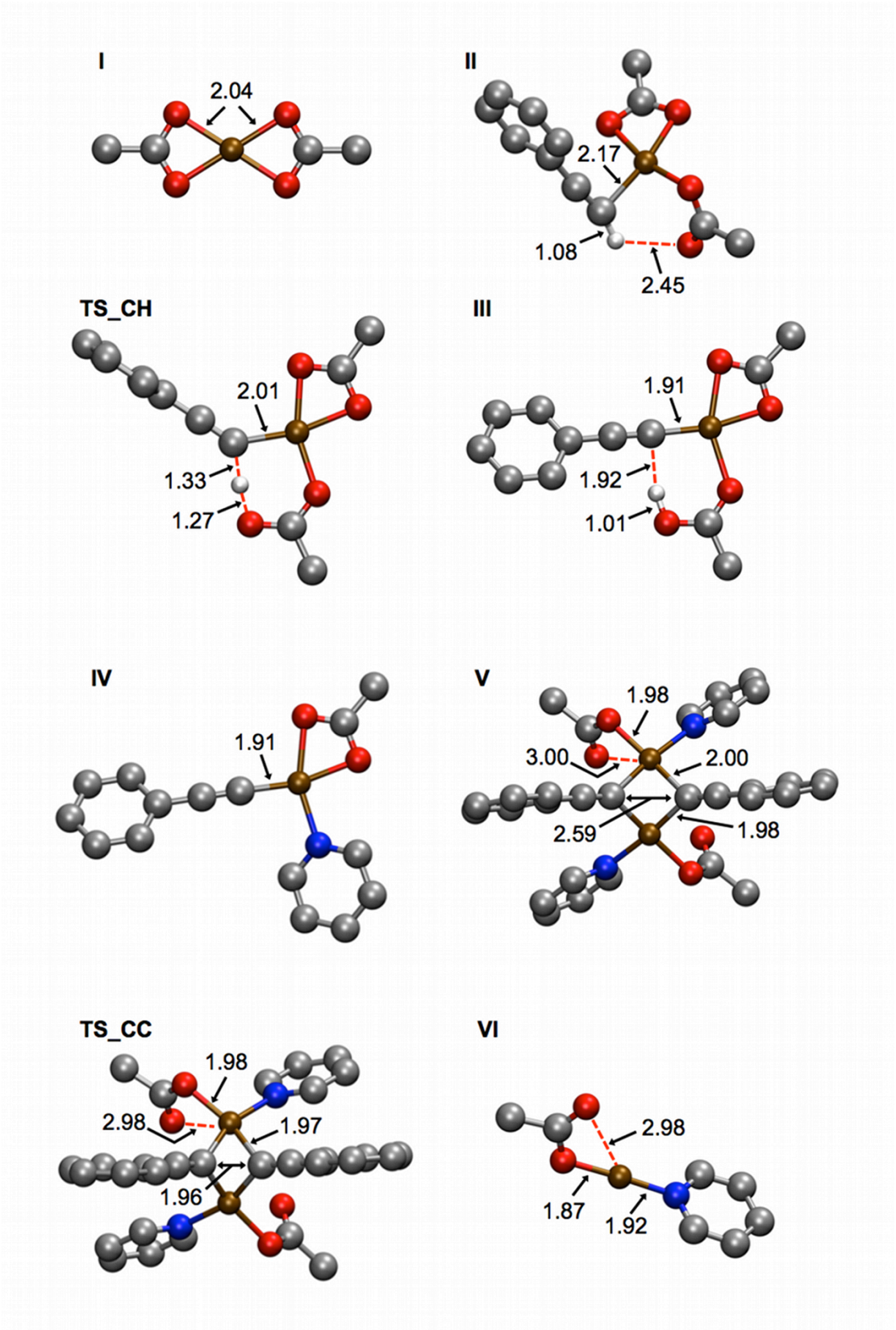


Figure 1. Detailed structures of **V** and **TS_CC** (distances in Å, Cu =brown, N = blue, O = red, C = gray, H =white; for clarity most H atoms have been omitted).

The catalytic cycle starts with the coordination of the terminal alkyne to copper(II) acetate (**I**) to form intermediate **II**. In this complex two new interactions are established, one between one of the acetate groups and the proton of the incoming alkyne and another one between the proximal carbon atom of the alkyne and the copper center. The O–H and Cu–C distances are 2.45 and 2.17 Å, respectively. Additionally, the alkyne C–H distance elongates to 1.08 Å after the coordination, making that bond slightly longer than that found in free phenylacetylene (1.04 Å). This process is not thermodynamically favored and almost 10 kcal mol^{-1} are required to attach the triple bond to the copper; this could be probably attributed to the worse donating ability of the triple bond when compared to the bidentate acetate group. Since intermediate **II** is higher in energy than **I**, and a strong structural rearrangement is required to get to the former, this step should be expected to depend on a transition state. All the attempts to directly locate this transition state failed and thus a linear transit energy scan was carried out to elucidate this part of the mechanism. This procedure, consisting of a series of optimizations where the distance between the substrate and the copper atoms is fixed at values between 2.2 and 2.9 Å, shows a monotonic uphill energy profile when the distance between both moieties decreases. These results seem to point out that, in principle, the addition of phenylacetylene onto **I** is not governed by a transition state. The particular arrangement of ligands in complex **II** facilitates the proton transfer between the alkyne and the pending acetate; in fact the deprotonation transition state (**TS_CH**) is less than 9 kcal mol^{-1} higher than **II** indicating this process should be quite fast. In **TS_CH** the Cu–C distance is reduced to 2.01 Å while the C–H and O–H distances become similar: 1.33 and 1.27 Å, respectively.

After the deprotonation intermediate **III** is obtained; this complex is slightly less stable than the previous one but remains at a reasonable height. In contrast, the direct deprotonation using pyridine as the base, as proposed in some reports, requires more than 35 kcal mol^{-1}. These results seem quite obvious since acetate is a stronger base than pyridine. In addition, the presence of the metal, once coordinated to the triple bond, contributes to enhance the acidity of the C–H bond and seems to be crucial in the proton transfer process. Once **III** is formed the reaction proceeds by the replacement of the newly formed acetic acid moiety by a pyridine molecule (**IV**). This process is thermodynamically favored and, since pyridine is the solvent and is present in great excess, it is expected to happen quite fast. The square planar intermediate **IV** is, in fact, the same species found in the left part of equation *ii* in Scheme 2. This complex, as all the other neutral mononuclear copper(II) species studied, has one unpaired electron and thus is in the doublet free energy surface. The spin distribution in **IV** indicates that the unpaired electron is mostly localized on the copper atom, although some spin polarization is found in the terminal carbon of the alkyne ligand. However, generating a free alkynyl radical and the corresponding [Cu(OAc)(py)] complex from **IV** is nearly impossible because that process requires more than 30 kcal mol^{-1}, probably because the alkynyl radical formed is not stable enough. In contrast, the dimerization of **IV** to deliver the dinuclear alkynyl-bridged complex **V** is thermodynamically viable. The formation of this complex forces the unpaired

electrons to couple, taking the reaction to the singlet free energy surface, which is, in turn, lower in energy than the triplet energy surface. Other dinuclear complexes *e.g.* acetate-bridged, produced higher energy intermediates. Both copper atoms in **V** have distorted square pyramidal structures, with one of the oxygen atoms of the acetate ligand occupying the axial position; the $Cu–O_{eq}$ and $Cu–O_{ax}$ distances are 1.98 and 3.00 Å, respectively. The Cu_2C_2 core in complex **V** is not completely planar but a wedge with alternated Cu–C distances of 1.98 and 2.00 Å, and a C–C distance of 2.59 Å. Since **V** is a singlet the spin distribution cannot be obtained; the open-shell analogous complex cannot be correctly computed with the B97D functional and thus the only way to obtain an estimation of the spin distribution requires the calculation of **V** in the triplet state. This calculation states that the unpaired electrons remain mainly on the copper atoms while only some spin delocalization can be found in the bridging alkynyl carbon atoms, ruling out the formation of the organic radicals proposed by Salkind and coworkers. From **V** the bimetallic reductive elimination process (**TS_CC**) is quite straightforward and requires only 2.6 kcal mol^{-1} to deliver the final diphenyldiacetylene product and the complex [Cu(OAc)(py)] (**VI)**. The geometry of this transition state is very similar to the one found for intermediate **V**, obviously the main differences are found in the Cu–C and C–C distances which shrink to 1.97 and 1.96 Å, respectively. Although the bimetallic reductive elimination is not a very common process it has already been proposed in the literature[35,39] and in the mechanism of Bohlmann and coworkers, which seems to be the right one to describe the reactivity of the studied reaction.

The calculations indicate that the reaction is exergonic by 25.9 kcal mol^{-1}. The highest barrier is 18.1 kcal mol^{-1}, computed as the free energy difference between **I** and **TS_CH**, and corresponding to the deprotonation process, which was proposed by Eglinton and Galbraith in their original paper as the rate-limiting step. This could explain why the more acidic acetylenes produce faster reactions. In order to check the validity of this statement the catalytic cycle was recomputed for two different substituted phenylacetylenes: *p*-$NO_2C_6H_4C{\equiv}CH$ and *p*-$MeC_6H_4C{\equiv}CH$. The computed results can be found in Figure 2.

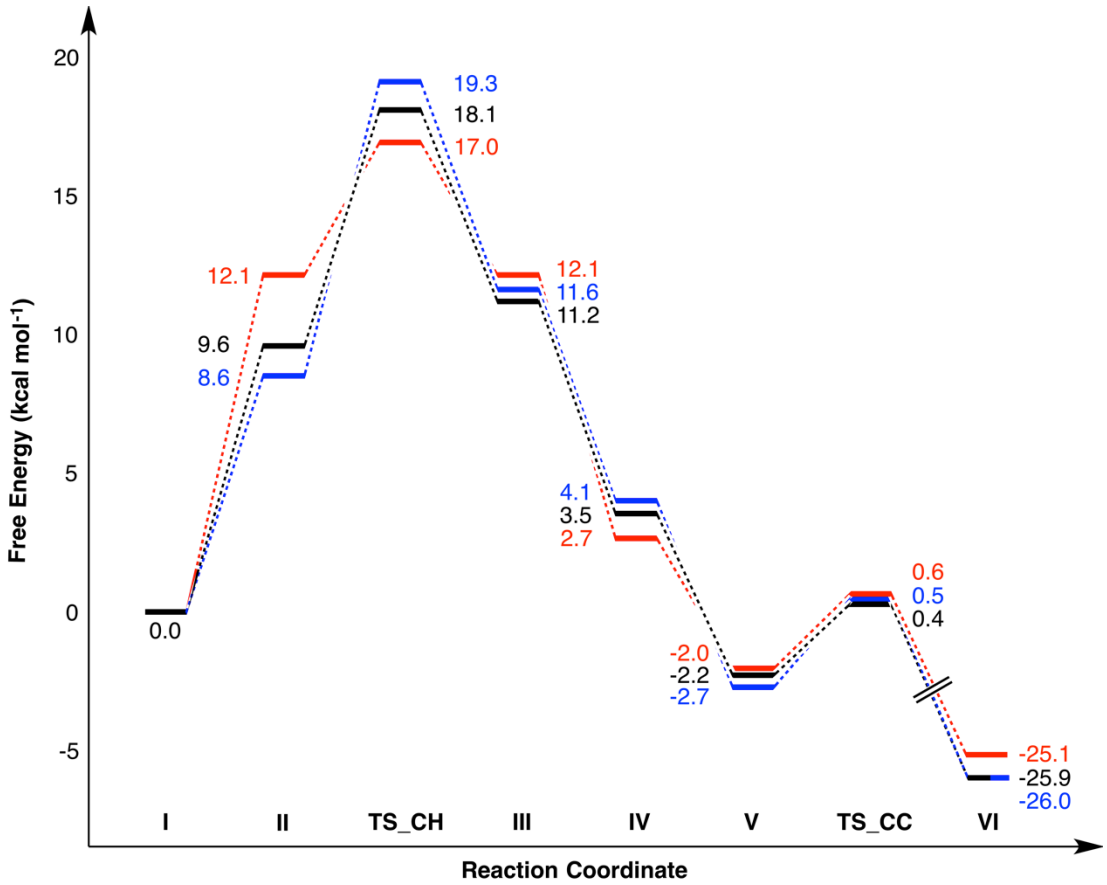


Figure 2. Computed free energy profiles for the different phenylacetylenes, color code: R = *p*-H (**black**), *p*-NO_2 (**red**) and *p*-Me (**blue**).

As may be observed the computed profiles for the three substrates follow a very similar trend. This should not be surprising because the geometries obtained for the catalytic cycle of the substituted phenylacetylenes are quite similar to those shown in Figure 1. In all cases the addition of the substrate on the copper(II) species **I** is endergonic and can be related to its donation ability *i.e.* the formation of complex **II** is more favorable for the most electron-rich substrate *p*-$MeC_6H_4C{\equiv}CH$. In contrast, the obtention of the same complex with *p*-$NO_2C_6H_4C{\equiv}CH$ requires an additional amount of 3.5 kcal mol^{-1}. The activation of the terminal C–H bond follows the reverse order, in agreement with the inductive effect of the *para*-group on the phenylacetylene. The deprotonation process requires 4.9, 8.5 and 10.7 kcal mol^{-1} for *p*-$NO_2C_6H_4C{\equiv}CH$, $C_6H_5C{\equiv}CH$ and *p*-$MeC_6H_4C{\equiv}CH$, respectively; indicating that the most electron-withdrawing substituents contribute to lower this transition state. In all cases a pyridine solvent molecule easily displaces the newly formed acetic acid, allowing the formation of complex **IV**. The dimerization of complex **IV**, as well as the reductive elimination transition state, has practically the same energy requirements for the three substituted phenylacetylenes. In all cases the highest barrier corresponds to the deprotonation step *i.e.* the free energy difference between **I** and **TS_CH**, which is 18.1, 17.0 and 19.3 kcal mol^{-1} for phenylacetylene, *p*-nitrophenylacetylene and *p*-metylphenylacetylene, respectively. The observed trend can be directly related to the acidity of the alkyne, as proposed by Eglinton and Galbraith, the acidic *p*-nitro

substituted substrate provides the lowest reaction barrier while the more electron-rich *p*-methyl substrate produces slower reactions because its deprotonation step has a higher free energy barrier.

Conclusions

The Eglinton oxidative homocoupling of terminal alkynes has been successfully studied using phenylacetylene as a model substrate. The calculations demonstrate that the coordination of the triple bond to the metal center enhances the acidity of the terminal C–H bond and facilitates its activation by the acetate ligand. The alternative deprotonation pathway using pyridine, the solvent of the reaction, as the base provides a much higher free energy profile and can be consequently ruled out.

The formation of the C–C bond is achieved from a dinuclear copper(II) complex with diradical character centered mainly on the metal atoms. This indicates that, in contrast to some of the classical proposals, the free organic alkynyl radicals are not formed. Consequently, the reaction proceeds following a mechanism that resembles the one proposed by Bohlmann and coworkers.

The highest free energy barrier for phenylacetylene corresponds to the deprotonation process, in agreement with the experimental observations. Calculations using different *para*-substituted phenylacetylenes also confirm that the most acidic substrates provide faster reactions because the deprotonation barrier is lower.

Conflict of Interests

The author declares that there is no conflict of interests regarding the publication of this paper.

Acknowledgment

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